IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF SOUTH CAROLINA
CHARLESTON DIVISION

IN RE: LIPITOR (ATORVASTATIN CALCIUM) MARKETING, SALES PRACTICES AND PRODUCTS LIABILITY LITIGATION	MDL No. 2:14-mn-2502-RMG
This document relates to: *Wilma Daniels v. Pfizer Inc.,* 2:14-cv-01400-RMG *Juanita Hempstead v. Pfizer Inc*., 2:14-cv-01879-RMG	

PLAINTIFFS' STEERING COMMITTEE MEMORANDUM OF LAW IN OPPOSITION TO PFIZER INC.'S MOTION TO EXCLUDE THE EXPERT TESTIMONY OF DAVID K. HANDSHOE, M.D.

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INTRODUCTION

In its motion to exclude the testimony of David Handshoe, M.D. that Lipitor was a substantial contributing factor in causing Wilma Daniels's and Juanita Hempstead's diabetes, Pfizer attempts to depict Dr. Handshoe as a physician with little or no experience in the diagnosis and treatment of diabetes, while portraying his opinions as biased and based on unreliable methodology. Both attacks are mischaracterizations: Dr. Handshoe is an internist who treats patients with diabetes and indeed diagnoses new-onset diabetes among his patients. Moreover, his opinions regarding the cause of Plaintiffs' diabetes are based in a sound methodology – differential diagnosis – which is supported by large bodies of medical and scientific literature. Pfizer's critique of Dr. Handshoe's methodology as "litigation-driven" is grossly inaccurate. Both medical practitioners and courts recognize differential diagnosis as a reliable tool for the determination of specific causation in individuals. Although Pfizer claims that Dr. Handshoe did not actually perform a differential diagnosis, examination of his report shows that Pfizer is wrong: the report shows the classic differential diagnosis, in which Dr. Handshoe "ruled in" Lipitor and other potential causes, and then systematically "ruled out" each other potential cause to arrive at his opinion that Lipitor was a "substantial contributing factor" to each Plaintiff's development of diabetes and that "but for [their] ingestion of Lipitor," they would not have developed diabetes. *See, e.g.,* Def. Ex. 7 at 9-11, 14.[1] Dr. Handshoe further testified at deposition that his methodology is no different from the differential diagnoses he utilizes every day in his clinical practice, when he considers all possible causes of a disease or condition and then rules out each possible cause until arriving at either the sole cause or the substantial contributing factor of the disease or condition. *See* Def. Ex. 6 at 186:4-23. Moreover, and significantly, Pfizer's experts used this same methodology in arriving at their contrary opinions. Pfizer may disagree with Dr. Handshoe's conclusions, but his qualifications and his methodology are unassailable.

[1] Wherever possible, Plaintiffs cite to exhibits submitted by Pfizer on this motion ("Def. Ex."), rather than resubmitting the same documents to this Court.

Pfizer also claims that Dr. Handshoe does not establish but-for causation. This of course has nothing to do with the reliability or admissibility of his opinion; it affects only the question of whether, assuming Dr. Handshoe's opinion and no other specific causation evidence is admitted at trial, Plaintiffs can meet their burden of proof. Indeed, Pfizer repeats this argument in its motion for summary judgment in the *Daniels* case. For the reasons set forth in Plaintiff Daniels's opposition to that motion, Pfizer is wrong about the burden of proof and about the nature of Dr. Handshoe's testimony. Moreover, that Dr. Handshoe cannot say whether either Plaintiff might eventually, years or decades later, have developed diabetes without Lipitor does not affect the validity of his opinion that, but for the Lipitor they took, they would not have developed diabetes when they did. As Dr. Handshoe's testimony makes clear, that is the meaning of his opinions; it is sufficient to prove but-for causation here. Nor does the fact that Dr. Handshoe offers his opinion "to a reasonable degree of medical certainty," rather than with 100% certainty, affect its admissibility.

At bottom, all of Pfizer's criticisms of Dr. Handshoe's opinions and methodology are weight-of-the-evidence arguments which Pfizer can make before the jury but which cannot support a motion to exclude. Dr. Handshoe's case-specific opinions are the product of reliable, accepted methodology and are well-supported by both the medical record in this case and extensive medical and scientific data and literature. They are admissible under Fed. R. Evid. 702. Pfizer's arguments should be addressed through "[v]igorous cross-examination, presentation of contrary evidence and careful instruction on the burden of proof." *Daubert v. Merrell Dow Pharms., Inc*., 509 U.S. 579, 596 (1993); they provide no basis to exclude Dr. Handshoe's opinions.

FACTUAL BACKGROUND

Type 2 Diabetes

Type 2 diabetes mellitus is caused by a combination of insulin resistance and impaired insulin secretion. Diabetes is characterized by elevated fasting blood glucose levels at or greater than 126 mg/dL, a glycated hemoglobin greater than or equal to 6.5%, and/or an oral glucose

tolerance test with glucose levels above 200 mg/dL after two hours. Laboratory values within diagnostic ranges must be repeated in order to confirm diagnosis. Individuals in whom insulin resistance has progressed, but whose blood glucose do not reach the threshold of diabetes are said to be prediabetic, meaning their fasting blood glucose levels are above normal, 100 mg/dL, but below the threshold for diabetes, 126 mg/dL. Type 2 diabetes typically results from dysregulation of glucose homeostasis—the balance of glucose and insulin necessary to maintain proper blood glucose. In other words, insulin resistance combined with impaired insulin secretion disrupts this balance and results in diabetes.

Genetic risk factors can predispose an individual to insulin resistance, impaired insulin secretion, and diabetes. Environmental factors can also contribute to the onset of new diabetes as well as the progression from prediabetes to diabetes. These environmental factors include, for example, diet, weight, inactivity, and the use of pharmaceutical drugs, like statins. Type 2 diabetes progresses from development of mild insulin resistance, leading to elevation of insulin levels that is sufficient to overcome the insulin resistance and normal blood glucose levels. As the body becomes less responsive to insulin, it manufacturers more insulin to compensate. Genetic factors combined with environmental factors, such as the use of statins, lead to insulin resistance worsening and fasting insulin levels rising even higher, resulting in diabetes.

A large body of scientific evidence shows that statins, and especially Lipitor, increase the risk of new onset Type 2 diabetes. (Indeed, the term "statin-induced diabetes" is well-known in the scientific literature. *See, e.g.*, Mark R. Goldstein & Luca Mascitelli, *Do Statins Cause Diabetes?*, Current Diabetes Reports, Vol. 13, No. 3, at 381-90 (June 2013) (Exhibit A); Annie L. Culver et al., *Statin Use and Risk of Diabetes Mellitus in Postmenopausal Women in the Women's Health Initiative*, Archives of Internal Med., Vol. 172, No. 2, at 144-52 (Jan. 23, 2012) (Exhibit B); Swapnil N. Rajpathak, MD, DRPH et al., *Statin Therapy and Risk of Developing Type 2 Diabetes: A Meta-Analysis*, Diabetes Care, Vol. 32, No. 10, at 1924-29 (Oct. 2009) (Exhibit C) It was not, as Pfizer suggests, coined by Dr. Handshoe for this litigation.) That evidence is discussed in detail in Plaintiffs' Steering Committee Memorandum of Law in Opposition to Pfizer's Motion

to Exclude Plaintiffs' Expert Testimony on the Issue of General Causation (Docket Entry #1047) ("General Causation Br."). Dr. Handshoe was aware of, and considered, much of this evidence in deciding to "rule in" Lipitor as a possible cause in both his expert reports, *see* Def. Ex. 7 at 7-9, Def. Ex. 39 at 7-8, before proceeding to discuss, and "rule out" potential alternative causes.

Wilma Daniels

As of the beginning of September, 1997, Wilma Daniels was a healthy, active woman who was working full-time. At 49 years old, she was somewhat overweight, but, with a body-mass index ("BMI") of 28, she was not obese. (According to the Centers for Disease Control and Prevention, a BMI of 25 or above is considered overweight, while a BMI of 30 or above is considered obese.) She stayed active through exercise and physical activity, including walking, aerobic exercise, sit-ups, and occasional dancing. Def. Ex. 7 at 9. She had normal blood glucose levels and did not have prediabetes[2] or diabetes. She had never had a stroke, heart attack, or chest pain, nor had she exhibited any objective or subjective signs of coronary artery disease. *See* Def. Ex. 21 at 120:3-121:12 and at 125:8-12. Furthermore, Defense expert Dr. Lopes-Virella admits that Ms. Daniels has never had a heart attack, stroke or been diagnosed with cardiovascular disease. Deposition of M. Lopes-Virella (Ex. D) at 116:24-117:9.

On September 4, 1997, she visited her primary care doctor, Dr. Kurt Wever, at Colorado Springs Health Partners ("CSHP"), in Colorado Springs, Colorado for a yearly checkup. Dr. Wever ordered lipid panels as part of his ordinary care which showed normal blood glucose levels[3], elevated total and LDL cholesterol, and elevated triglycerides. Dr. Wever diagnosed Ms. Daniels

[2] In August, 1997, Ms. Daniels had a single blood glucose reading above 125 mg/dL which was drawn when she reported to the ER after losing consciousness at work. This isolated level reflected a transient phenomenon known as "stress hyperglycemia," in which an individual's glucose levels rise as a result of trauma or stress. More importantly, this blood glucose reading was *not* in the abnormal range because it was a non-fasting value. Def. Ex. 32 at 36:4-7.

[3] Ms. Daniels blood glucose was 108 mg/dL at the time of this visit, however, Dr. Wever confirmed that the lab results did not indicate that the values were fasting. Def. Ex. 32 at 42:1-5. Again, as a non-fasting value, this glucose level was normal.

with essential hypercholesterolemia at that time and, one month later, started her on a mid-strength dosage of Lipitor (40mg).

In September 1998, a physician's assistant at Ms. Daniels's doctor's practice ordered a test of her blood glucose level. This was the first time anyone had tested her blood sugar since she had begun to take Lipitor the previous fall. The test showed a random blood glucose level of 169 mg/dL with an HbA1c, a week later, of 6.1%.[4] A month later, her glucose remained elevated at 143 mg/dL. Neither of these tests appears to have been a fasting test, meaning that both values put Ms. Daniels squarely in the pre-diabetes range. On October 21, 1988, Dr. Wendy Day diagnosed Ms. Daniels with new-onset "borderline" diabetes, by which she appears to have meant prediabetes, which was consistent with her non-fasting glucose values and her A1C value, which was also below the threshold for diabetes. At the time Dr. Day diagnosed her as prediabetic, Ms. Daniels's total cholesterol was 212; her LDL cholesterol was 113. Both values were above the desirable, target levels, which call for total cholesterol under 200 and LDL cholesterol under 100. In other words, after taking Lipitor for approximately one year, Ms. Daniels' cholesterol remained elevated but her blood glucose had risen to a prediabetic level.

Ms. Daniels' blood sugar continued to rise over the next several years as she continued to take Lipitor. Finally, Ms. Daniels' HbA1c increased to 6.9% in November 2003, thereby exceeding the diagnostic criteria for diabetes as defined by the NIH and the American Diabetes Association. She was still taking Lipitor for her cholesterol.

Juanita Hempstead

Juanita Hempstead is a retired school principal who suffers from hypertension and dyslipidemia. Ms. Hempstead began seeing Dr. Lou Sabih at the Parkway Family Care Center in Lee's Summit, Missouri, in January 1998. In March, 1998, Dr. Sabih obtained a lipid panel, the results of which showed total cholesterol of 243 mg/dL, LDL cholesterol of 151 mg/dL, and

[4] Ms. Daniels' lab results do not indicate whether they are fasting or non-fasting values, however, Ms. Johnson's notation in the medical records specifically indicate a *random* – not fasting – blood glucose test. A "random" glucose test indicates that the patient has not been fasting.

triglycerides of 255. All of these values were elevated and Dr. Sabih prescribed Lipitor 20 mg daily in response to these labs results. Because of her concerns about possible liver toxicity associated with Lipitor, Ms. Hempstead did not start taking the Lipitor at that time.

Approximately one year later, in June, 1999, Dr. Sabih ordered another lipid panel. This time, Ms. Hempstead's total cholesterol was 250 and her LDL was 175, although her triglycerides had declined to 143. Ms. Hempstead was again prescribed Lipitor 20 mg daily; she began taking it sporadically, refilling her prescription in December, 1999, and again in July of 2000. At the time Ms. Hempstead was prescribed Lipitor in June, 1999, she was 55 years old and, with a BMI of 26.4, only slightly overweight but not obese.

In October, 2000, Dr. Michael Ausmus became Ms. Hempstead's primary care physician. Beginning in July, 2000, Ms. Hempstead took the Lipitor she was prescribed regularly (with a three week hiatus in the fall of 2003 because of abdominal pains). In February, 2004, Ms. Hempstead went to the Emergency Room for nausea, vomiting and bloody diarrhea. Laboratory testing revealed a random (that is, a non-fasting) blood glucose of 214 mg/dL. She was discharged with the diagnosis of colitis.

On May 14, 2004, approximately two weeks before her sixtieth birthday, Ms. Hempstead again went to the Emergency Room; this time, she was admitted to the hospital with a blood glucose level of 613 mg/dL and a diagnosis of new-onset type 2 diabetes. Her A1C was 12.2%. She was hospitalized for three days, treated with insulin, and received diabetes education. Although no accurate weight was noted at the time of her hospitalization, at the first follow-up after hospital discharge, Ms. Hempstead had a BMI of 27.0, still overweight. Ms. Hempstead has never been obese.

David Handshoe, M.D.

Dr. David Handshoe has practiced medicine for approximately thirty years. He graduated *cum laude* from Millsaps College in Jackson, Mississippi, in 1980 with a Bachelor of Science degree in biology and received his medical degree from the University of Mississippi School of

Medicine in 1984. He is a Board Certified Physician in the areas of Internal Medicine, Pulmonary Diseases, Critical Care Medicine, and Sleep Disorders.

He performed his internship and residency in Internal Medicine at the University of Michigan Hospitals in Ann Arbor, Michigan (1984-1987). He then practiced internal medicine for three years in rural Mississippi, where he cared for indigent patients, including patients with diabetes on a daily basis. Afterward, he performed a Pulmonary/Critical Care fellowship at Duke University Medical Center in Durham, North Carolina, from 1990 to 1993.

After his Duke training, Dr. Handshoe moved to Charleston, South Carolina where he currently practices internal medicine, pulmonary, critical care, and sleep medicine at Lowcountry Lung and Critical Care and also at South Carolina Sleep Medicine. He is also on the active medical staff of Trident Health System, including Trident Medical Center, and of Charleston Surgery Center. He serves as Medical Director of ICUs and is member of the Critical Care Committee for Trident Health System. He is licensed in South Carolina, Mississippi, and North Carolina. He has participated as principal investigator or sub-investigator in dozens of clinical trials.

Dr. Handshoe's practice in internal medicine includes assisting patients with the prevention, diagnosis, and treatment of a number of medical conditions, particularly chronic conditions and complications arising therefrom. His experience includes the diagnosis and treatment of patients with Diabetes Mellitus (Type 1 and Type 2). In his current medical practice, he see patients with Type 1 and Type 2 Diabetes Mellitus daily.

Dr. Handshoe prepared two expert reports in this matter, one pertaining to Wilma Daniels, the other pertaining to Juanita Hempstead.[5] He used the same methodology to prepare the two reports. In each case, he based his report on review of scientific literature, analysis of clinical trial data, other expert reports, his education, training, clinical experience, and the medical records of the Plaintiff who is the subject of the report. *See* Def. Ex. 7 at 2, Def. Ex. 39 at 2. His reports show

[5] Dr. Handshoe is the only expert offered by Wilma Daniels on the issue of specific causation. Juanita Hempstead offers both Dr. Handshoe and Dr. Elizabeth Murphy, whose opinions are the subject of a separate motion to exclude by Pfizer (and a separate response by Ms. Hempstead).

that he cited and relied on a vast amount of scientific literature; the depositions of each of the Plaintiffs, as well as their doctors and, in Ms. Daniels's case, a family member; and the totality of their medical records. *See* Handshoe First Amended List of Materials Considered and Relied Upon in *Daniels* and *Hempstead* (Ex. E); Def. Ex. 7; Def. Ex. 39. In his report for Ms. Daniels, he provides the following opinion:

> Based on my review of Ms. Daniels' medical records, the relevant scientific medical literature, the reports prepared by other experts in this case, and my medical training and clinical experience, it is my opinion that Lipitor was a substantial contributing factor to Ms. Wilma Daniels' development of Type 2 Diabetes Mellitus, and, but for her ingestion of Lipitor, Ms. Daniels would not have developed Type 2 Diabetes Mellitus. All opinions expressed herein are to a reasonable degree of medical certainty.

Def. Ex. 7 at 14. Similarly, with respect to Ms. Hempstead, Dr. Handshoe opines:

> Based on my review of Ms. Hempstead's medical records, the relevant scientific medical literature, the reports prepared by other experts in this case, and my medical training and clinical experience, it is my opinion that Lipitor was a substantial contributing factor to Ms. Juanita Hempstead's development of Type 2 Diabetes Mellitus, and, but for her ingestion of Lipitor, Ms. Hempstead would not have developed Type 2 Diabetes Mellitus. All opinions expressed herein are to a reasonable degree of medical certainty.

Def. Ex.39 at 14.

In forming these opinions, Dr. Handshoe performed differential diagnoses. *See* Def. Ex. 7 at 4-7, 9-11; Def. Ex. 39 at 4-7, 8-11. He determined that each plaintiff had taken Lipitor and had thereafter developed diabetes, both in terms of laboratory values and symptoms. He then considered whether each plaintiff "developed Type 2 Diabetes Mellitus as a result of genetic and environmental factors or whether her use of Lipitor was a substantial contributing factor, without which she would not have developed insulin resistance and a decreased production of insulin from beta cells, thereby leading to her diabetes." Def. Ex. 7 at 7; *see also* Def. Ex. 39 at 7. Considering the scientific evidence, he "ruled in" Lipitor as a potential cause. Def. Ex. 7 at 7-9; Def. Ex. 39 at 7-8. Finally, he considered other potential causes – including weight, level of activity, ethnicity, age, polycystic ovary syndrome, gestational diabetes, smoking (in the case of Ms. Hempstead) and family history – and ruled each one out as sufficient, by themselves or in combination, to account

for the plaintiff's diabetes. Def. Ex. 7 at 9-11; Def. Ex. 39 at 8-11. This is the standard "differential diagnosis" technique. *See infra* at 14-15. Dr. Handshoe did not – and did not need to – *entirely* rule out each of the other factors, because he concluded that multiple factors could have contributed to Ms. Hempstead's and Ms. Daniels's diabetes. Rather, Dr. Handshoe ruled out the possibility that these other factors *alone* were sufficient to cause Plaintiffs' diabetes. He concluded that Lipitor was a substantial contributing cause and that but for taking Lipitor, Ms. Daniels and Ms. Hempstead would not have developed diabetes. Def. Ex.7 at 14; Def. Ex. 39 at 14. Although the opinions in his reports are stated without qualification, at his depositions, Dr. Handshoe clarified that his opinions are that each plaintiff would not have developed diabetes *when she did* had she not taken Lipitor. He does not presume to know whether, at some later date in the future, either Plaintiff might have independently become diabetic. As discussed below, this clarification in no way affects the validity of Dr. Handshoe's opinions and, indeed, it actually strengthens them.

LEGAL STANDARDS

Federal Rule of Evidence 702 governs the introduction of expert opinion testimony: Expert testimony is admissible under Rule 702 "if it concerns (1) scientific, technical, or other specialized knowledge that (2) will aid the jury or other trier of fact to understand or resolve a fact at issue." *Westberry v. Gislaved Gummi AB*, 178 F.3d 257, 260 (4th Cir. 1999) (citing *Daubert*, 509 U.S. at 592). The second prong of the inquiry requires an analysis of whether the opinion is relevant to the facts at issue. *Id*.

The first prong of this inquiry necessitates an examination of whether the reasoning or methodology underlying the expert's proffered opinion is reliable—that is, whether it is supported by adequate validation to render it trustworthy. *Id. (citing Daubert* at 590 & n. 9). In *Daubert*, the Supreme Court identified four non-dispositive factors to consider when determining whether or not the reasoning behind an expert's testimony is reliable: (1) whether the theory presented has been or can be tested; (2) "whether the theory…has been subjected to peer review and publication"; (3) "the known or potential rate of error"; and (4) the amount of acceptance given to the expert's

reasoning or methodology within the relevant professional community. *Daubert*, 509 U.S. at 593-594.

The *Daubert* test is flexible; "[r]ather than providing a definitive or exhaustive list, *Daubert* merely illustrates the types of factors that will bear on the inquiry." *United States v. Crisp*, 324 F.3d 261, 266 (4th Cir. 2003). As the Court of Appeals for the Fourth Circuit has noted: "In making its initial determination of whether proffered testimony is sufficiently reliable, the court has broad latitude to consider whatever factors bearing on validity that the court finds to be useful; the particular factors will depend upon the unique circumstances of the expert testimony involved." *Westberry,* 178 F.3d at 261.

The *Daubert* Court was careful to emphasize that the "overarching subject" of the Rule 702 inquiry "is the scientific validity – and thus the evidentiary relevance and reliability – of the principles that underlie a proposed submission." 509 U.S. at 594-95. Accordingly, the Court explained, "[t]he focus … must be solely on principles and methodology, not on the conclusions that they generate." *Id.* at 595. The Fourth Circuit has echoed this caution. *TFWS, Inc. v. Schaefer*, 325 F.3d 234, 240 (4th Cir. 2003) ("In applying *Daubert*, a court evaluates the methodology or reasoning that the proffered scientific or technical expert uses to reach his conclusion; the court does not evaluate the conclusion itself."); *Westberry*, 178 F.3d 261. ("The inquiry to be undertaken by the district court is 'a flexible one' focusing on the 'principles and methodology' employed by the expert, not on the conclusions reached"). Nothing in Rule 702 or *Daubert* and its progeny, or in the rulings of the Fourth Circuit permits this Court to subject an expert's conclusions, as opposed to his methodology, to the *Daubert* analysis. Indeed, the Fourth Circuit has made clear that "the court need not determine that the expert testimony a litigant seeks to offer into evidence is irrefutable or certainly correct." *Id*.

Daubert does not require the subject of scientific testimony to be "'known' to a certainty," since science is an evolving process, and "arguably there are no certainties in science." *Daubert*, 509 U.S. at 590. The Supreme Court has recognized that there is a "range where experts might reasonably differ, and where the jury must decide among the conflicting views of different

experts." *Kumho Tire Co., Ltd. v. Carmichael*, 526 U.S. 137, 153 (1999). The Court's function is simply to "make certain that an expert, whether basing testimony upon professional studies or personal experience, employs in the courtroom the same level of intellectual rigor that characterizes the practice of an expert in the relevant field." *Id.* at 152.

In addition to prescribing fluid and general standards for the admission of scientific testimony, "*Daubert* also described the trial court's role as that of a 'gatekeeper' who should exercise broad discretion in admitting scientific testimony that could later be tested by '[v]igorous cross-examination, presentation of contrary evidence, and careful instruction on the burden of proof....'" *Id*. (quoting *Daubert* at 596). Plaintiffs do not "have to prove their case twice—they do not have to demonstrate to the judge by a preponderance of the evidence that the assessments of their experts are *correct*, they only have to demonstrate by a preponderance of evidence that their opinions are reliable." *Maryland Cas. Co. v. Therm-O-Disc, Inc*., 137 F.3d 780, 783 (4th Cir. 1998) (internal citations omitted) (emphasis in original). "A review of the case law after *Daubert* shows that the rejection of expert testimony is the exception rather than the rule." *Palmetto Pharm. LLC v. AstraZeneca Pharm. LP*, 2014 WL 1334215, at *4 (D.S.C. Apr. 2, 2014), citing Fed. R. Evid. 702, Advisory Committee's Note to 2000 Amendments).

The gatekeeper role, moreover, is not intended to supplant the adversary system or the role of the jury; rather, "[v]igorous cross-examination, presentation of contrary evidence, and careful instruction on the burden of proof are the traditional and appropriate means of attacking shaky but admissible evidence." *Daubert*, 509 U.S. at 596. Indeed, the Fourth Circuit has recognized that "Rule 702 was intended to liberalize the introduction of relevant expert evidence." *Westberry*, 178 F.3d at 261.

ARGUMENT

I. DR. HANDSHOE IS QUALIFIED TO OFFER HIS OPINIONS

Contrary to Pfizers' assertions, Dr. Handshoe is highly qualified to offer expert opinions as to the cause of Plaintiffs' diabetes, even though he is not an endocrinologist. Rule 702 of the

Federal Rules of Evidence provides in pertinent part that "[a] witness who is qualified as an expert by knowledge, skill, experience, training, or education may testify in the form of an opinion . . . ." Fed. R. Evid. 702. The Fourth Circuit has cautioned against reading this requirement too narrowly, *Belk, Inc. v. Meyer Corp., U.S.*, 679 F.3d 146, 162 (4th Cir. 2012), as amended (May 9, 2012), and noted that the court "should . . . consider the proposed expert's full range of experience and training, not just his professional qualifications." *Id.* Thus, numerous courts recognize that, as the First Circuit has held, "[t]he fact that the physician is not a specialist in the field in which he is giving his opinion affects not the admissibility of his opinion but the weight the jury may place on it." *Mitchell v. United States*, 141 F.3d 8, 15 (1st Cir. 1998), *accord Gaydar v. Sociedad Instituto Gineco-Quirurgico y Planificacion*, 345 F.3d 15, 24 (1st Cir. 2003) ("[t]he proffered expert physician need not be a specialist in a particular medical discipline to render expert testimony relating to that discipline."); *see also McDowell v. Brown*, 392 F.3d 1283, 1297 (11th Cir. 2004) (same); *United States v. Garcia*, 7 F.3d 885, 890 (9th Cir.1993) (witness's "lack of particularized expertise goes to the weight accorded her testimony, not to the admissibility of her opinion as an expert"); *McCullock v. H.B. Fuller Co.*, 61 F.3d 1038, 1043 (2nd Cir. 1995) (doctor need not be a specialist in the precise area of medicine implicated by the plaintiff's injury); *In re Chantix (Varenicline) Products Liability Litigation*, Case No. 2:10-CV-1463-IPJ, at 33 (N.D. Ala. September 18, 2012) (Exhibit F) ("so long as the expert has some specialized knowledge as a result of training or experience relevant to the opinions he offers, his testimony will meet the qualification requirement"); *Floyd ex rel. Ray v. United States*, 3:08-CV-122 CDL, 2010 WL 4905010 (M.D. Ga. Nov. 26, 2010).

Here, Dr. Handshoe's knowledge and expertise qualify him as an expert able to provide testimony helpful to the jury. Dr. Handshoe has been a practicing physician for approximately 30 years. He is board-certified in internal medicine and sees patients with diabetes on a daily basis, often diagnosing new onset diabetes and regularly treating diabetics in an interim capacity until his patients can be seen by their primary care physicians. *See* Def. Ex. 6 at 54:14-55:6 (sees and treats diabetes everyday), at 57:21-25 (treats diabetes while in ICU), at 58:16-24 and at 72:25-73:9

(diagnoses and treats diabetes regularly), and at 74:22-23 ("a whole spectrum of diabetes care is delivered in the intensive care unit"). Internists are described by the American Board of Medical Specialties as being "trained in the diagnosis and treatment of cancer, infections and diseases affecting the heart, blood, kidneys, joints and the digestive, respiratory and vascular systems. They are also trained in the essentials of primary care internal medicine, which incorporates an understanding of disease prevention, wellness, substance abuse, mental health and effective treatment of common problems of the eyes, ears, skin, nervous system and reproductive organs." *See* Exhibit G. Endocrinology, which focuses on diabetes and other disorders of the internal glands, is considered a subspecialty of internal medicine. *Id.*[6]

Dr. Handshoe's practice follows a six-week rotation with two weeks of that time dedicated to working in the Intensive Care Unit ("ICU") of a local hospital, one week doing consultations at two local hospitals, two weeks working in his office practice, and one week off. Def. Ex. 6 at 48:19-49:15. Given the fact that diabetes as a disease process affects the overall function of the body as a whole, even at molecular levels, Dr. Handshoe naturally must stay informed and abreast of developments regarding this disease since the care that he provides at a pulmonary/critical care level is often intricately related to and affected by diabetes, along with numerous chronic disease processes, such as hypertension, hypothyroidism, high cholesterol, etcetera. Likewise, since Dr. Handshoe is board certified in internal medicine, it is essential that he remain current on medical topics pertinent to that area of practice, including diabetes. Given the fact that Dr. Handshoe regularly diagnoses and treats diabetes and regularly studies developments related to diabetes in the normal course of his practice, it is proper that he describes himself as an expert in the "biological mechanism by which diabetes develops." *Id*. at 70-71.

As a medical doctor, moreover, Dr. Handshoe has the requisite training to read and interpret medical articles, as he did in rendering his opinions here. As another MDL court has explained in

[6] Indeed, Plaintiff Hempstead's other specific causation expert, Dr. Elizabeth Murphy, who *is* an endocrinologist specializing in diabetes testified at her deposition that "any healthcare provider, for example, can diagnose diabetes." *See* Def. Ex. 18 at 76:9-10.

rejecting a challenge to the opinions of a practicing physician who relied in part on scientific articles relevant to his field, "Dr. Fine does not have to be a toxicologist, chemist, radiologist and/or have personally conducted animal studies to be able read, understand, interpret and rely upon the published literature of those experts on the science related to his field of expertise in order to offer an opinion." *In re Gadolinium-Based Contrast Agents Products Liab. Litig.*, No. 1:08 GD 50000, 2010 WL 1796334, at *18 (N.D. Ohio May 4, 2010) *opinion modified on other grounds on reconsideration*, No. 1:08 GD 50000, 2010 WL 5173568 (N.D. Ohio June 18, 2010), *aff'd sub nom. Decker v. GE Healthcare Inc.*, 770 F.3d 378 (6th Cir. 2014). Indeed, as the court explained, "it is vital for physicians like Dr. Fine to keep up with the literature on subjects that bear on their field of expertise in order to ensure they are properly and safely caring for their patients," thus ensuring that the expert's review of scientific literature in that case was entirely consistent with his general practice.

Dr. Handshoe is thus qualified by reasons of his knowledge, his experience, his training, and his education to offer an opinion about the cause Plaintiffs' diabetes.

II. DR. HANDSHOE PROPERLY PERFORMED A DIFFERENTIAL DIAGNOSIS WITH RESPECT TO EACH PLAINTIFF

Pfizer contends that Dr. Handshoe did not perform differential diagnoses, that if he did, he did them improperly, and that his opinions are based entirely on temporal proximity. None of this is true.

A. Dr. Handshoe's Opinions Are Based on Differential Diagnoses

In reaching his specific causation opinion, Dr. Handshoe utilized the well-accepted differential diagnosis methodology to determine that Lipitor caused both Ms. Daniels's and Ms. Hempstead's diabetes. Differential diagnosis, also known as differential etiology, is a "standard scientific technique of identifying the cause of a medical problem by eliminating the likely causes until the most probable one is isolated." *Westberry*, 178 F.3d at 262. Thus, in *Westberry*, the Fourth Circuit specifically held that "*a reliable differential diagnosis provides a valid foundation for an expert opinion*." *Id.* at 263 (emphasis added). The Court noted that the technique "has

widespread acceptance in the medical community, has been subject to peer review, and does not frequently lead to incorrect results." 178 F.3d at 262–63, *quoting In re Paoli R.R. Yard PCB Litig*., 35 F.3d 717, 758 (3d Cir. 1994); *see also Glaser v. Thompson Med. Co*., 32 F.3d 969, 978 (6th Cir. 1994) (recognizing that differential diagnosis is "a standard diagnostic tool used by medical professionals to diagnose the most likely cause or causes of illness, injury and disease"). Indeed, as the Fourth Circuit has recognized, "the overwhelming majority of the courts of appeals that have addressed the issue have held that a medical opinion on causation based upon a reliable differential diagnosis is sufficiently valid to satisfy the first prong of the Rule 702 inquiry." *Westberry*, 178 F.3d at 263, *citing Heller v. Shaw Indus., Inc*., 167 F.3d 146, 154, 156-7 (3d Cir.1999) (concluding that a proper differential diagnosis is adequate to support expert medical opinion on causation); *Kennedy v. Collagen Corp*., 161 F.3d 1226, 1228–30 (9th Cir. 1998) (holding district court abused its discretion in excluding an expert opinion on causation based upon a reliable differential diagnosis); *Baker v. Dalkon Shield Claimants Trust*, 156 F.3d 248, 252–53 (1st Cir. 1998); (determining that a differential diagnosis rendered expert opinion on causation sufficiently reliable for admission); *Zuchowicz v. United States*, 140 F.3d 381, 385–87 (2d Cir. 1998) (upholding determination that expert opinion was reliable in part based on differential diagnosis); *Ambrosini v. Labarraque*, 101 F.3d 129, 140–41 (D.C.Cir. 1996) (holding that because expert opinion was based on differential diagnosis, district court abused its discretion in refusing to admit it).

A reliable differential diagnosis "is accomplished by determining the possible causes for the patient's symptoms and then eliminating each of these potential causes until reaching one that cannot be ruled out or determining which of those that cannot be excluded is the most likely." *Westberry*, 178 F.3d at 262. In the simplest of terms, differential diagnosis amounts to a "ruling in" of possible causes followed by the "ruling out" of each of these causes until the most likely cause remains.

Here, Dr. Handshoe thoroughly reviewed the medical records of each plaintiff, the deposition testimony of each plaintiff and her medical providers, and the medical literature

concerning diabetes before undertaking his differential diagnosis. Moreover, Dr. Handshoe testified that the differential diagnoses he performed with respect to Ms. Daniels and Ms. Hempstead used the same method he uses every day, contrary to Pfizer's assertions that his methodology is "litigation-driven." *See, e.g.* Def. Ex. 6 186:4-23. Indeed, he "routinely" uses the identical differential diagnosis to determine the cause of diabetes in patients he sees in the intensive care unit. *Id*. at 187:5-17.

1. *Dr. Handshoe Performed a Differential Diagnosis With Respect to Ms. Daniels*

Dr. Handshoe began his differential diagnosis by considering whether he could "rule in" Lipitor as a possible cause of Ms. Daniels's diabetes. He considered whether (a) Ms. Daniels had taken Lipitor; (b) whether in fact she met the standard criteria for the diagnosis of diabetes; (c) whether she had symptoms consistent with that diagnosis; and (d) whether Lipitor can cause diabetes. *See* Def. Ex. 7 at 3-9. He determined each of these criteria was met. Then, as he explains, "in order to confirm a diagnosis of statin-induced Type 2 Diabetes Mellitus, other types of diabetes must be ruled out." *Id.* To do this, he identified, or "ruled in," potential alternative causes of diabetes: weight, level of activity, family history, race/ethnicity, age, polycystic ovary disease, and other medications, including, in particular in Ms. Daniels's case, diuretics such as hydrochlorothiazide ("HCTZ"), all of which he identified as risk factors and potential causes of diabetes. *Id.* at 6.

In ruling out the potential alternative causes, both individually and in combination, Dr. Handshoe analyzed each such alternative cause, discussing its relevance to Ms. Daniels. He found, for example, that although she was heavier at the onset of her first symptoms at 1998, her body mass index when she began taking Lipitor was 28, which is overweight, but not obese. He also noted that she was active, engaging in a variety of types of exercise and physical activity, such as walking, aerobic exercises, sit-ups and dancing. Apart from these exercise activities, Dr. Handshoe found that Ms. Daniels's active daily routine additionally minimized the amount to which her weight was a factor in the development of her diabetes: he noted that she performed

housework, cared for children and grandchildren, worked full-time and enjoyed such social activities as bowling. *Id.* at 9. For these reasons, he found her weight insufficient to explain her diabetes. Dr. Handshoe found that Ms. Daniels did not fit into any racial or ethnic group at especially high risk of diabetes. *Id.* He further noted that, at 50, her age did not place her at significant risk of diabetes. *Id.* He found that although she was taking a diuretic, HCTZ, the dose she was taking, and the fact that she did not have a concurrent potassium deficiency (hypokalemia), a tell-tale risk factor for HCTZ-elevated blood sugars, made the HCTZ an unlikely cause of her diabetes. *Id.* at 6-7; Def. Ex. 6 at 247:6-16. Finally, he ruled out polycystic ovary disease and gestational diabetes as well. Def. Ex. 7 at 9.

Dr. Handshoe acknowledged that Ms. Daniels had some family history of diabetes (one sibling (out of five) with Type 2 diabetes and one child (out of four) with Type 2 diabetes), but found that history insufficient to explain her development of diabetes at the time of diagnosis. *Id.* at 11. Significantly, Dr. Handshoe further explained at his deposition that the diagnosis of Type 2 diabetes in Ms. Daniels's daughter would be even less likely to suggest family history as a cause of Ms. Daniels's diabetes if Ms. Daniels's ex-husband (her daughter's father) also had a family history of diabetes. Def. Ex. 6 at 287:22-288:1. In fact, Ms. Daniel's daughter, Denise Austin, did testify that her father (Ms. Daniels's ex-husband) had a significant family history that included two of her father's brothers and her father's mother, *see* Deposition of D. Austin (Ex. H) at 30:22-31:11, thus confirming Dr. Handshoe's view that Ms. Daniels's family history, as least as reflected in her daughter, was unlikely to be the sole cause of her diabetes.

Nonetheless, it is clear that, in concluding that Lipitor was a "substantial contributing factor" in her diagnosis of diabetes, Dr. Handshoe recognized that her weight and family history may have played a role, even if alone they would not have caused her diabetes at the time she developed it. Def. Ex. 7 at 9, 11.

Thus, Dr. Handshoe's differential diagnosis has "take[n] serious account of other potential causes" as mandated by the law of the Fourth Circuit. *Cooper v. Smith & Nephew, Inc.*, 259 F.3d 194, 202 (4th Cir. 2001) (*quoting Westberry*, 178 F.3d at 265). As discussed below, Pfizer's

criticisms of the specifics of that diagnosis can and should be addressed through "[v]igorous cross-examination, presentation of contrary evidence and careful instruction on the burden of proof." *Daubert*, 509 U.S. at 596. Dr. Handshoe's opinions are clearly within "the range where experts might reasonably differ," and the jury, not the trial court, should be the one to "decide among the conflicting views of different experts." *Kumho Tire*, 526 U.S. at 153.

2. *Dr. Handshoe Performed a Differential Diagnosis With Respect to Ms. Hempstead*

Dr. Handshoe performed a similar differential diagnosis with respect to Juanita Hempstead's diabetes. The first part of his analysis, where he "ruled in" Lipitor as a potential cause of Ms. Hempstead's diabetes, was essentially the same as the "ruling in" process in his differential diagnosis for Ms. Daniels. *See* Def. Ex. 39 at 4-6, 77-8. The "ruling out" process, although similar, was individualized to Ms. Hempstead's medical records and testimony. Dr. Handshoe identified the same potential alternative causes: weight, level of activity, family history, race/ethnicity, age, polycystic ovary disease, and other medications, again noting the use of HCTZ. *Id.* at 6.

Again, to rule out the potential alternative causes, both individually and in combination, Dr. Handshoe analyzed each such alternative cause, discussing its relevance to Ms. Hempstead. He was of the opinion that Ms. Hempstead's weight and BMI at diagnosis were not a substantial contributing factor to Ms. Hempstead's diabetes, reasoning that, with a BMI of 28.6, she was "only slightly overweight," and that her extra weight was sufficiently counter-balanced by her high level of activity and health-conscious lifestyle. As a school principal, she regularly walked the stairs, halls and premises of her school. *See* Def. Ex. 36 at 41:13-42:18. She also watched her diet, exercised regularly at a local gym, and went on long walks approximately three times per week. *Id*. at 172:23-173:2. Dr. Handshoe placed special significance on Ms. Hempstead's extremely active lifestyle because it would have offered a protective benefit against the development of diabetes in the face of her being slightly overweight. Def. Ex. 39 at 9.

Dr. Handshoe considered Ms. Hempstead's age at diagnosis (59 years old) and concluded that it was not a substantial contributing factor for her development of diabetes. *Id.* at 10. At deposition, he recognized that a woman at the age of 59 would have a minor increase in the risk of diabetes, but he considered it not to be the "major driver of her diabetes." Def. Ex. 41 at 143:2-16. He further reiterated that he "ruled out" her age, because, based upon his research, her age was "not significant." *Id*. at 142:10-20.

Dr. Handshoe also considered Ms. Hempstead's multiracial heritage and ruled it out as a substantial contributing factor to the development of her diabetes. Ms. Hempstead's multiracial background includes African-American, Choctaw Indian and Franco-Caucasian heritages. Dr. Handshoe recognized that, had she been of 100% African-American heritage, she would have been at a slightly increased risk of developing diabetes. Def. Ex. 39 at 10. However, owing to her mixed heritage, Dr. Handshoe reasoned that the risk posed by her partial African-American heritage was even less significant. Def. Ex. 41 at 140:13-19. Dr. Handshoe also considered Ms. Hempstead's Choctaw Indian heritage but ultimately ruled it out as a contributing factor to her diabetes. Importantly, his opinion in this arena was based upon his first-hand knowledge from three-years of internal medicine practice in rural Mississippi: "[B]ased on my clinical experience of working in rural Mississippi where the Choctaw Nation is from, I did not see an increased incidence of diabetes in Choctaw Indians." *Id*. at 139:19-23.

Dr. Handshoe considered whether Ms. Hempstead's family history was a substantial contributing factor in the development of her diabetes, and he ruled that out as well: Ms. Hempstead's father developed diabetes late in his 80s and none of Ms. Hempstead's seven siblings has diabetes. Def. Ex. 39 at 9. He also excluded polycystic ovary disease and gestational diabetes, because Ms. Hempstead had never suffered from these. *Id.* at 10. Dr. Handshoe also ruled out Ms. Hempstead's remote light smoking history: Ms. Hempstead had quit smoking years before she developed diabetes and had never been a heavy smoker to begin with. *See* Def. Ex. 36 at 128:9-21. Moreover, as he explained at his deposition, "[t]he association of women [and smoking] is

quite – is much smaller than men and based on her smoking history of a few cigarettes a week, I would say this is completely insignificant." Def. Ex. 41 at 146:25-147:4.

As was true for Ms. Daniels, Dr. Handshoe ruled out the HCTZ Ms. Hempstead took because of her low dosage and the fact that she, like Ms. Daniels did not have concurrent hypokalemia, as required for the HCTZ to affect her blood glucose levels. *Id.* 41 at 180:25-181:24; Def. Ex. 39 at 6. Moreover, Dr. Handshoe found that the impact of HCTZ on blood sugar, when it does occur, is too small to explain the extreme elevation of Ms. Hempstead's blood glucose level at the time of her diagnosis. *Id*.

While Pfizer may disagree with any, or all, of these judgments, there can be no doubt that Dr. Handshoe performed a differential diagnosis, carefully "ruling in" and "ruling out" the various potential causes of diabetes to arrive at his conclusion that "Ms. Hempstead's ingestion of Lipitor was a substantial contributing factor in her being diagnosed with new onset Type 2 Diabetes Mellitus." Def. Ex. 39 at 11. Based on his differential diagnosis, Dr. Handshoe's opinion is clearly within "the range where experts might reasonably differ," and the jury, not the trial court, should be the one to "decide among the conflicting views of different experts." *Kumho Tire*, 526 U.S. at 153.

B. Dr. Handshoe's Opinions Are Not Based Solely on Temporal Proximity

1. *Dr. Handshoe's Consideration of the Temporal Association Among Other Factors Was Limited and Proper*

Pfizer insists that Dr. Handshoe's opinions are based solely on the temporal proximity between plaintiffs' ingestion of Lipitor and subsequent development of diabetes. To be sure, Dr. Handshoe did consider temporal proximity in reaching both his opinions, and in the end it was the most significant factor for him. But that was true only because he had ruled out so many other factors for reasons entirely unrelated to temporality. It is simply not the case that Dr. Handshoe's opinions are based entirely on temporal proximity.

Dr. Handshoe ruled out polycystic ovary syndrome and gestational diabetes because both were completely absent. He ruled out HCTZ based on both the dosage and the absence of

hypokalemia. He ruled out inactivity because both Ms. Daniels and Ms. Hempstead were physically active. He ruled out weight/BMI for both Ms. Hempstead and Ms. Daniels because Ms. Hempstead was not obese when she was diagnosed, and Ms. Daniels was not obese when she began taking Lipitor. *See* Def. Ex. 7 at 9-11; Def. Ex. 39 at 8-11. Similarly, he discounted family history because the history was so slight – in Ms. Daniels case, one brother (out of five siblings) and a daughter who more likely inherited it from her father's side where the family history was more pronounced, and in Ms. Hempstead's case, only her father who, significantly, did not develop the disease until he was over the age of 80. Def. Ex. 7 at 11; Def. Ex. 39 at 9-10. By the time he had ruled out so many other causes, it is hardly surprising that the temporal proximity of Lipitor usage to the development of diabetes loomed large in Dr. Handshoe's remaining analysis. Moreover, as discussed below, he did not rule out factors like weight and family history as *contributing* causes; he ruled out only the possibility that Lipitor was not a substantial factor and had not made the difference. *See infra* at 28.

Consideration of the temporal relationship as one factor among others is entirely proper. As the Fourth Circuit has explained, "[D]epending on the circumstances, a temporal relationship between exposure to a substance and the onset of a disease or a worsening of symptoms can provide *compelling evidence of causation*." *Westberry,* 178 F.3d at 265(emphasis added) (finding that a doctor's testimony based on differential diagnosis and the temporal connection to exposure to talc sufficient to establish specific causation). The same is true here, but it does not mean that Dr. Handshoe failed to consider other factors and other possible causes.

Pfizer's reliance on two cases from the Fifth and Eleventh Circuits regarding temporality is misplaced and distinguishable. In *Moore v. Ashland Chem. Inc*., 151 F.3d 269, 278 (5th Cir. 1998), the Fifth Circuit indeed held that "the temporal connection between exposure to chemicals and an onset of symptoms, *standing alone*, is entitled to little weight in determining causation." (emphasis added). Again, temporality was hardly the sole factor considered by Dr. Handshoe. Furthermore, the Court in *Moore* placed particular importance on the fact that the excluded expert relied on only one published study to support his causation opinion and that the relied-upon study's

authors themselves made "clear that their conclusions were speculative because of the limitations of the study." *Id.* Here, Dr. Handshoe relied upon numerous published studies as well as plaintiffs' general causation experts in formulating his opinions, and his opinions are thus entirely distinguishable from those in *Moore*.

Guinn v. AstraZeneca Pharm. LP, 602 F.3d 1245 (11th Cir. 2010) is similarly distinguishable. In *Guinn*, plaintiffs' expert was unaware, at the time she formed her opinion, of much of the plaintiff's medical history, including her weight fluctuations, her "sedentary lifestyle, a poor diet, a significant family history of diabetes, hypertension, hyperlipidemia, schizophrenia, and prediabetes." 602 F.3d at 1249. The expert in *Guinn* failed even to consider these factors, since she did not even know about them. Moreover, and most significantly here,

> When asked what she had done to rule out Guinn's other risk factors as the sole cause of Guinn's diabetes, Dr. Marks stated *she knew of no methodology for ruling out alternative causes and thus had not attempted to do so*. In fact, Dr. Marks agreed Guinn's other risk factors alone were sufficient to explain the onset of her diabetes. Dr. Marks stated, however, she had "no way of ruling out the Seroquel any more than she could rule out any other risk factors."

Id. at 1249-50 (emphasis added). Indeed, the expert in *Guinn* admitted that "she could not rule out the possibility that Guinn had diabetes before ever taking Seroquel." *Id.* at 1250.

Here, by contrast, Dr. Handshoe was fully aware of, and considered, all of Plaintiffs' medical and family histories. *See* Def. Ex. 7 at 9-11; Def. Ex. 39 at 8-11. Far from claiming he could not rule out other causes, Dr. Handshoe specifically ruled out several alternative causes, and analyzed those that could have contributed to Plaintiffs' diabetes. *Id.* Moreover, while the expert in *Guinn* agreed that other risk factors *alone* were sufficient to explain the plaintiffs' diabetes there, Dr. Handshoe here specifically found that the other risk factors were insufficient and that "but for her ingestion of Lipitor [Plaintiff] would not have developed Type 2 Diabetes Mellitus." Def. Ex. 7 at 11; Def. Ex. 39 at 14.

2. *Dr. Handshoe Correctly Assessed the Factor of Temporal Proximity*

Pfizer also contends that, to the extent Dr. Handshoe considered temporality at all, he did it wrong, because, Pfizer contends, diabetes takes at least a decade to develop and each Plaintiff

took Lipitor for only approximately five years before her diabetes diagnosis. Pfizer is wrong for three reasons. First, estimates of the amount of time over which diabetes develops vary. Dr. Edwin Gale, whose testimony Pfizer cites in support of its "at least a decade" argument, actually testified that scholarly estimates of the time for diabetes to develop had been in the range of five to ten years, but were now "on the shorter end of that range." Def. Ex. 1 at 174:5-175:10. Dr. Elizabeth Murphy, also an endocrinologist and diabetes specialist, testified that in her opinion, based on her experience, the time period is approximately three to five years, although she acknowledged it could be longer. *See* Def. Ex. 18 at 83:23-84:18. Even assuming the validity of Pfizer's argument, using the estimates reported by Dr. Gale and Dr. Murphy, Dr. Handshoe's consideration of temporal proximity was right on target.

But Pfizer's argument is invalid for two other reasons. It assumes that Lipitor does not *accelerate* the diabetes process. But, as described in Plaintiffs' Causation Brief, that is precisely what Lipitor can do. *See* General Causation Br. at 35. As Plaintiffs' general causation expert, Dr. Michael Quon, stated in his report, "[a]torvastatin therapy unequivocally increases insulin resistance and/or glucose intolerance. . . ." Def. Ex. 45 at 20. A person in whom insulin resistance or glucose intolerance is gradually developing will thus have those processes intensified by exposure to Lipitor, shortening the time period from the inception of the disease process to its manifestation in a case of full-blown diabetes.

Finally, Pfizer is wrong because it assumes that Lipitor cannot "cause" diabetes unless it *initiates* the disease process in a completely healthy individual. That is not so as a matter of medicine, as a matter of common parlance, or most significantly, as a matter of law. Because Plaintiffs need not show that Lipitor was the sole cause of their diabetes, they need not show that it was the initial, or original cause. A substantial contributing factor is sufficient. *See Smith v. State Comp. Ins. Fund*, 749 P.2d 462, 464 (Colo. App. 1987) (to prevail on causation, plaintiff must show that defendant's conduct was a "substantial factor" in producing the harm); *Hagen v. Celotex Corp*., 816 S.W.2d 667, 670 (Mo. 1991) ("substantial factor" test); *Nesselrode v. Executive Beechcraft, Inc.*, 707 S.W.2d 371, 381 (Mo. 1986) ("the proximate cause of an event or injury need

only be a substantial factor or efficient causal agent"). Moreover, courts have long recognized that "a tortfeasor is fully liable for any damages resulting from its wrongful act even if the victim had a pre-existing condition that made the consequences of the wrongful act more severe for him than they would have been for a person without the condition." *McLaughlin v. BNSF Ry. Co*., 2012 COA 92, ¶ 35, 300 P.3d 925, 934-35 (Colo. Ct. App. June 7, 2012); *see also Miller v. Gulf, M. & O. R. Co.*, 386 S.W.2d 97 (Mo. 1964) ("a defendant is generally liable for the aggravation of pre-existing conditions caused by his negligence.") Thus, a "tortfeasor may not escape or reduce liability because the victim's pre-existing condition made him more susceptible of injury from the tortfeasor's conduct." *McLaughlin,* 300 P.2d at 935. Even if the diabetes disease process had begun in either or both of the Plaintiffs before they started taking Lipitor, Lipitor may still have caused their diabetes if it made the difference between that process progressing to diabetes, or not progressing, or in the amount of time it took to progress. In this regard, it is significant that, as the Centers for Disease Control recognizes, "not everyone with prediabetes will progress to diabetes." *See* Exhibit I. Indeed, Dr. Murphy testified that, while there is tremendous individual variation, among patients with prediabetes "[i]n general, 20 to 25 percent progress to diabetes over five years. . . 50 percent remain prediabetic, and another 25 percent of the patients resolve their prediabetes." Def. Ex. 18 at 105:9-106:1. Pfizer's experts gave similar testimony. *See* Deposition of M. Lopes-Virella (Exhibit J) at 50:18-51:9 (two-thirds of patients with impaired glucose tolerance do not develop diabetes); Deposition of K. Spratt (Exhibit K) at 160:19-22 (not everyone with prediabetes will develop diabetes); Deposition H. Glassberg (Exhibit L) at 73:22-74:1 (same). Because so many of those with prediabetes[7] do not go on to develop diabetes, Pfizer is simply wrong when it argues that Lipitor cannot cause diabetes in anyone in whom the process has already begun. For

[7] There is, of course, no evidence in this case that either Plaintiff had prediabetes before beginning to take Lipitor. Indeed, Wilma Daniels was diagnosed with "borderline diabetes," apparently (given the lab values involved) a synonym for prediabetes, for the first time one year *after* she started taking Lipitor.

all these reasons, Pfizer's contention that Dr. Handshoe got the temporal relationship between Lipitor and diabetes "wrong" should be rejected.

C. Pfizer's Disagreement with the Specific Factors Dr. Handshoe Ruled In and Ruled Out Provides No Basis to Exclude His Opinions

Pfizer takes issue with the specific details of Dr. Handshoe's differential diagnosis, quibbling with the factors he "ruled in" and those he "ruled out." This amounts to little more than Pfizer's contention that it disagrees with Dr. Handshoe and would have done the analysis differently. The question whose differential diagnosis is more persuasive is not, however, a matter to be resolved by the Court in its gate-keeping role; it is, rather, a matter to be resolved by a jury. Moreover, if Dr. Handshoe failed to rule out a factor Pfizer believes should have been considered, failure to rule out every possible alternative cause is not fatal to the admissibility of a differential diagnosis. *Westberry*, 178 F.3d at 265 (a "medical expert's causation conclusion should not be excluded because he or she has failed to rule out every possible alternative cause of a plaintiff's illness.").

For example, Pfizer believes that Dr. Handshoe gave too little weight to smoking as a potential cause of diabetes. Dr. Handshoe did give his opinion on the impact a woman's smoking has on the possibility of her developing diabetes during one of his depositions. Dr. Handshoe testified that he read multiple medical studies on the connection between smoking and diabetes. There seemed to be no clear consensus, as some of the journal articles he read suggested that smoking causes diabetes and others did not make such a suggestion. He further noted that the association was much less significant in women. Def. Ex. 41 at 146:17-147:4. For this reason, Dr. Handshoe opined that that Ms. Hempstead's remote light smoking history was "completely insignificant." *Id*. at 146:4. Ms. Daniels, too, had a smoking history that was remote – she had quit eight years before being diagnosed with diabetes. *See* Def. Ex. 21 at 132:16-21. Notably, at least some of Pfizer's experts also did not consider smoking a relevant factor. *See* Exhibit L at 110:5-7 (so far as expert is aware, smoking does not increase the risk of diabetes); Exhibit J at 54:20-55:8 (explaining why smoking "didn't make my cutoff for a major factor"). Plaintiffs'

treaters agree. *See*, *e.g.,* Def. Ex. 30 at 65:13-24 (smoking not a risk factor for diabetes); Def. Ex. 44 at 79:11-15 (evidence equivocal as to whether smoking is a risk factor for diabetes). Dr. Handshoe's failure to give weight to this smoking history does not render his differential diagnosis unreliable.

Similarly, Pfizer argues that Dr. Handshoe did not properly rule out Ms. Hempstead's ethnic heritage as a contributing factor to her diabetes because he was unaware of a 1993 study finding that there was an increased incidence of diabetes in Choctaw Indians. Such a position is a classic weight-of-evidence argument that is clearly the province of the jury. Apart from his first-hand experience that indicated to him that Choctaws did not have an increased incidence of diabetes, Dr. Handshoe also seriously questioned the applicability of this study to Ms. Hempstead because she was of mixed heritage and not pure Choctaw. Def. Ex. 41 at 205:22-206:5. It should be left to the jury to determine whether it gives more weight to Dr. Handshoe's experience and reasoning or to Pfizer's proffered study. *See, e.g., Lust v. Clark Equipment Co*., 792 F.2d 436, 439 (4th Cir. 1986) (It is "for the jury to decide which of the experts was more credible, which used the most reliable data, and whose opinion – if any – the jury would accept."); and *United States v. Lamarr*, 75 F.3d 964, 973 (4th Cir. 1996) (recognizing "a fundamental rule of the jury system is that this court is bound by the credibility choices of the jury.") (internal citations omitted).

Pfizer also claims that Dr. Handshoe failed to rule in metabolic syndrome for either Plaintiff. Metabolic syndrome is a cluster of conditions — increased blood pressure, high blood sugar levels, excess body fat around the waist and abnormal cholesterol levels — that occur together; some people believe metabolic syndrome increases the risk of diabetes. Others question whether the syndrome itself increases the risk beyond the increase associated with each factor. Dr. Murphy, for example, testified that she did not consider metabolic syndrome a helpful construct and did not believe there was sufficient evidence that lumping the symptoms together resulted in any additive risk. *See* Def. Ex. 18 at 249:18-251:6.

While Dr. Handshoe did not specifically utilize the term "metabolic syndrome," he did consider its components in performing his differential diagnosis. The three components of

metabolic syndrome that Pfizer considers to be at play in Ms. Daniels's medical history are elevated triglycerides, low high-density lipoprotein and hypertension. *See generally* Def. Ex. 6 231:5-235:22. Dr. Handshoe makes clear in his deposition that he recognizes that those three factors imply that she has metabolic syndrome but that he did not specifically mention the term. *Id.* at 235:19-22. However, it is clear from his report and his deposition testimony that he is of the opinion that Ms. Daniels's elevated triglycerides, low high-density lipoprotein and hypertension were not substantial contributing factors to the development of her diabetes. He discusses the various medical reports noting her elevated triglycerides. He mentions her varying low and normal levels of low high-density lipoprotein. He discusses hypertension and its treatment. However, he does not consider these to be substantial contributing factors to Ms. Daniels diabetes. *See generally* Def. Ex. 7 at 3; Def. Ex. 6 at 237:2-9.

In the case of Ms. Hempstead, Dr. Handshoe did not "rule in" or consider metabolic syndrome because he does not believe that Ms. Hempstead had metabolic syndrome in the first place. Pfizer contends that Ms. Hempstead had the requisite hypertension, elevated blood glucose (>100 mg/dL) and low HDL to support a diagnosis of metabolic syndrome, but Dr. Handshoe strongly disagrees that Ms. Hempstead met the criteria of metabolic syndrome before she began taking Lipitor and developed diabetes and thus did not "rule in" metabolic syndrome as a possible cause of Ms. Hempstead's diabetes. Dr. Handshoe's opinion that Ms. Hempstead did not have metabolic syndrome was based on a careful analysis of her glucose levels before she started to take Lipitor. He further strongly objected to Pfizer's use of lab values from different periods of time – such as a blood glucose level from April 1995 and an HDL cholesterol reading from June 1999 – to establish that she had metabolic syndrome, which would require the component conditions to occur simultaneously. He testified: "You [Pfizer's lawyer] can, again, cherry pick things from different times and different lab [reports], but I do not believe she had the metabolic syndrome, no." Def. Ex. 41 at 179: 18-22.

Pfizer's contentions concerning the role of stress and the possible involvement of Ciproflaxin, a medication that Ms. Hempstead took, similarly belong to the realm of cross-

examination, and provide no grounds for exclusion. In both instances, Dr. Handshoe provided detailed explanations for why he did not consider those factors causative, *see* Def. Ex. 6 at 271: 6-14; Def. Ex. 41 at 72:4-74:6, 187:9-88:20; it should be left to the jury to decide if those explanations are sufficient.

It is also true that Dr. Handshoe did not entirely eliminate all of the possible alternative causes, because he recognized that factors such as weight and family history, and in Ms. Hempstead's case, her race, might all play a role. But a differential diagnosis need not entirely exclude other contributing factors, especially where, as here, Dr. Handshoe does not opine that Lipitor was the sole cause of Plaintiffs' diabetes, only that it was a "substantial contributing factor." *Id.* at 14. In *Cooper*, for example, the Fourth Circuit made clear that a reliable differential diagnosis must consider alternative causes or "offer an explanation for why the proffered alternative cause was not the *sole cause*." 259 F.3d at 202 (emphasis added), *citing Westberry*, 178 F.3d at 265-66); *see also In re Paoli R.R. Yard PCB Litig*., 35 F.3d at 758 n.27. The Eleventh Circuit similarly has held that an admissible differential diagnosis "must consider other factors that could have been the *sole cause* of the plaintiff's injury." *Guinn*, 602 F.3d at 1253-55 (emphasis added). These cases show that a differential diagnosis need not rule out alternative causes entirely, only that it must show that these alternatives were not the sole cause. That is precisely what Dr. Handshoe did here, when he ruled out all of the other causes, separately or in combination as the sole cause of Plaintiffs' diabetes and concluded not only that Lipitor was a substantial contributing factor, but also that, but for the Lipitor, Plaintiffs would not have developed diabetes when they did. Moreover:

> A medical expert's opinion based upon differential diagnosis normally should not be excluded because the expert has failed to rule out every possible alternative cause of a plaintiff's illness. In such cases, *the alternative causes suggested by a defendant normally affect the weight that the jury should give the expert's testimony and not the admissibility of that testimony*.

Cooper, 259 F.3d at 202 (emphasis added); *see also Daubert*, 509 U.S. at 596 ("Vigorous cross-examination, presentation of contrary evidence, and careful instruction on the burden of proof are

the traditional and appropriate means of attacking shaky but admissible evidence."); *Freeman v. Case Corp*., 118 F.3d 1011 (4th Cir. 1997) (recognizing that the introduction of contrary theories is one of the appropriate means of discrediting allegedly suspect expert testimony). The time for Pfizer to attack Dr. Handshoe's opinions will be at trial when he can be cross-examined and when Pfizer can present its testimony to contradict his opinions; however, his opinions should not be excluded at this juncture.

D. **Pfizer's Experts Used the Same Methodology as Dr. Handshoe**

One of the most striking aspects of Pfizer's case specific expert reports is that they too, perform differential diagnoses in arriving at their opinions that Lipitor did not cause the diabetes of either Ms. Daniels or Ms. Hempstead. Of course, none of Pfizer's experts state that they performed a differential diagnosis, but even a cursory glance at their opinions demonstrates that each case specific expert "ruled in" numerous possible alternative causes of each plaintiff's diabetes (although, oddly never ruling in Lipitor) and then determined that none of those possible alternative causes should be ruled out. Plaintiffs do not dispute that Pfizer's experts may offer their opinions as to why they did not rule out, for example, Ms. Daniels's family history or Ms. Hempstead's BMI. However, Plaintiffs should similarly be allowed to present Dr. Handshoe's opinions as to why he did rule out those same possible alternative causes. As the Fourth Circuit has recognized, "the court need not determine that the expert's proffer is irrefutable or certainly correct. In liberalizing the standard for admission, *Daubert* reminds us that, as with all other admissible evidence, expert testimony is subject to being tested by '[v]igorous cross-examination, presentation of contrary evidence, and careful instruction on the burden of proof.'" *Bourne ex rel. Bourne v. E.I. DuPont de Nemours & Co*., 85 F. App'x 964, 966-67 (4th Cir. 2004) (internal citations omitted) (*quoting Daubert*, 509 U.S. at 596). In fact, it is "for the jury to decide which of the experts [is] more credible, which used the most reliable data, and whose opinion – if any – the jury would accept." *Lust v. Clark Equipment Co*., 792 F.2d 436, 439 (4th Cir. 1986).

For example, Pfizer's expert Dr. Kelly Spratt considered many of the same possible alternative causes for Ms. Daniels' diabetes that Dr. Handshoe considered, including metabolic

syndrome, sedentary lifestyle, weight gain, and family history, but declined to rule these factors out. *See* Spratt *Daniels* Report (Ex. M) at 11. She also declined to "rule in" Lipitor as a risk factor despite recognizing that "several studies have reported a slightly increased risk of both hyperglycemia and newly diagnosed diabetes mellitus in patients on statin therapy." *Id*. Clearly, Dr. Handshoe and Dr. Spratt disagree, but given the similarity of their methodology, their opinions are undoubtedly within "the range where experts might reasonably differ," and the jury, not the trial court, should be the one to "decide among the conflicting views of different experts." *Kumho Tire*, 526 U.S. at 153.

Similarly, Dr. Tom Elasy "ruled in" numerous risk factors including Ms. Daniels's "weight, age, hypercholesterolemia, hypertension, physical and emotional stressors, and family history." Def. Ex. 25 at 2. He declined to "rule in" Lipitor as a possible cause of Ms. Daniels's diabetes. *Id.* at 6. He makes clear that he rules out none of these possible alternative causes by concluding that "[s]he has many classic risk factors for diabetes that readily explain her diabetes disease development." *Id.* at 7. Thus, Dr. Elasy considered Ms. Daniels's medical history, isolated possible causes of her diabetes ("ruled in") and then examined whether any could be ruled out (in his opinion, none could). This is precisely what Dr. Handshoe did, only with different conclusions.

The same is true in the case of Dr. Maria Lopes-Virella, who offers opinions with respect to both Ms. Daniels and Ms. Hempstead. In both cases, she "ruled in," and then did not "rule out" certain factors that Dr. Handshoe believed could be ruled out, while refusing to "rule in" Lipitor as a possible cause. *See generally* Lopes-Virella *Daniels* Rpt. (Ex. N) and Lopes-Virella *Hempstead* Rpt. (Ex. O). These are all issues where Dr. Handshoe simply disagrees with Pfizer's experts, as discussed above. Dr. Lopes-Virella did not rule these factors out; Dr. Handshoe does. Again, such disagreements set up a classic battle of the experts; they are not a proper basis for the exclusion of either Pfizer's experts or Dr. Handshoe.

Dr. Helene Glassberg also "ruled in" multiple factors but declined to rule any of them out with respect to Juanita Hempstead. Glassberg *Hempstead* Rpt. (Ex. P) at 2. Those risk factors that Dr. Glassberg declined to rule out – metabolic syndrome, hypertension, elevated triglycerides, low

HDL, weight gain and ethnicity – were all addressed by Dr. Handshoe; he and Dr. Glassberg simply disagree on their importance. *Id*. Again, hardly surprisingly, Dr. Glassberg refused to "rule in" Lipitor as a possible contributing factor to Ms. Hempstead's development of diabetes despite failing to explain her reasoning for not doing so. Rather, Dr. Glassberg merely makes conclusory statements related to Lipitor such as "atorvastatin did not cause or contribute to cause her diabetes" without any support or even token explanation. *Id.* at 10. Nevertheless, the weight of Dr. Glassberg's opinions and their methodology (and its similarity to Dr. Handshoe's methodology) should ultimately be weighed by the jury in keeping with the tenets of *Daubert* and its progeny. The remainder of Pfizer's case-specific experts similarly considered precisely the same causes, and used nearly the same "ruling in, ruling out" process, to reach their conclusions. *See generally* S. Waikar *Hempstead* Rpt. (Ex. Q); M. Miller *Hempstead* Rpt. (Ex. R); V. Fonseca *Hempstead* Rpt. (Def. Ex. 40); and T. Garvey *Hempstead* Rpt. (Ex. S). Their use of the same methodology further demonstrates the soundness of Dr. Handshoe's work.

E. It Was Not Necessary for Dr. Handshoe to Examine Plaintiffs In Order to Form His Opinions

Pfizer claims that Dr. Handshoe's opinions are inadmissible because he "deviate[d] from his own typical practice whereby he seeks firsthand knowledge by examining and interviewing patients." *See* Pfizer Br. at 33. This argument is, frankly, silly. While his normal practice is to physically examine a patient presenting with an undiagnosed condition, that simply was not possible here because *both Plaintiffs' symptoms of diabetes began over ten years ago*. Moreover, having been diagnosed with diabetes in 2003 and 2004, both Plaintiffs have, since then, controlled their symptoms with oral medications. Therefore, a physical examination of either Plaintiff would have yielded no additional information helpful to Dr. Handshoe's differential diagnosis. The only way Dr. Handshoe could have performed a physical examination comparable to what he does in his own clinical practice would have been to use a time-machine to go back to 2003 and 2004 and examine Ms. Daniels and Ms. Hempstead at the time of their diagnoses.

Moreover, while courts have recognized that differential diagnosis may include a physical examination, among other analyses, they have also found that "a physician may reach a reliable differential diagnosis without himself performing a physical examination, particularly if there are other examination results available. In fact, it is perfectly acceptable, in arriving at a diagnosis, for a physician to rely on examinations and tests performed by other medical practitioners." *Kannankeril v. Terminix Int'l, Inc*., 128 F.3d 802, 807 (3d Cir. 1997), as amended (Dec. 12, 1997) (emphasis added). That is exactly what Dr. Handshoe did in Plaintiffs' cases. Because a physical examination of each would have proven unhelpful to Dr. Handshoe's differential diagnosis, he instead relied upon Plaintiffs' detailed medical records, containing contemporaneous notes taken by their respective physicians (upon physical examinations of Ms. Daniels and Ms. Hempstead), which described various physical symptoms and laboratory results, among other pertinent information that allowed Dr. Handshoe to perform a thorough and reliable differential diagnosis of each plaintiff. Additionally, despite Pfizer's adamant assertions that an expert's failure to perform a physical examination of a patient renders a differential diagnosis fundamentally unreliable, its own experts had no qualms whatsoever in performing what were, essentially, their own differential diagnoses concerning the cause of both Plaintiffs' diabetes without the benefit of a physical examination of either Ms. Daniels or Ms. Hempstead.

F. Dr. Handshoe's References to the Hill Factors Do Not Render His Opinions Inadmissible

Pfizer claims that Dr. Handshoe's opinions of specific causation should be excluded because of his discussion of the so-called Hill factors, used to determine if an association found in epidemiological studies is in fact causal.[8] But Pfizer fails to note that Dr. Handshoe's specific causation opinions stand on the basis of the differential diagnoses alone and do not depend on the Dr. Handshoe's discussion of the Hill factors, which he took to be confirmatory. *See* Def. Ex. 7

[8] The Hill factors, named for Dr. Austin Bradford Hill, are nine factors that epidemiologists commonly use to assess causation. *See* REFERENCE MANUAL ON SCIENTIFIC EVIDENCE at 600-606; *see also* General Causation Br. at 9.

at 11; Def. Ex. 39 at 11. Indeed both reports present their conclusions before any mention whatsoever of the Hill criteria. *Id.* Pfizer ignores, as well, that in order to rule in Lipitor as a possible cause of Plaintiffs' diabetes, it was necessary for Dr. Handshoe to consider the question of general causation. In this regard, it was not inappropriate for him to consider the Hill factors. Indeed, his discussion of the Hill factors reflects the epidemiological evidence he considered on the question of general causation. Whether his discussion of the Hill factors would pass muster as a general causation opinion, moreover, is beside the point: Plaintiffs offer the opinions of four other experts on the subject of general causation. Dr. Handshoe's efforts to confirm their work do not render his case-specific differential diagnoses unreliable or inadmissible.

III. DR. HANDSHOE OFFERS OPINIONS SUFFICIENT TO SHOW BUT-FOR CAUSATION

Pfizer claims that Dr. Handshoe does not offer a "but for" causation opinion with respect to Ms. Daniels, because he cannot rule out the possibility that Ms. Daniels would have developed diabetes "at some point" even if she had not taken Lipitor. *See* Pfizer Br. at 29-30. Pfizer makes this same argument in its motion for summary judgment in the *Daniels* case. Plaintiff Wilma Daniels fully addresses the argument in her brief in opposition to that motion ("Pltf. MSJ Opp."), which Plaintiffs here incorporate by reference. Plaintiffs note here that "but for" causation does not require that a plaintiff prove that, but for her use of Lipitor, she would *never* have developed diabetes, any more than a plaintiff who loses a limb through a defendant's negligence is required to show that she would not later have lost the limb under other circumstances. *See* Pltf. MSJ Opp. at Point IIA2. Dr. Handshoe appropriately testified no one could possibly know whether or not Wilma Daniels would have eventually developed diabetes decades from now had she never ingested Lipitor. *See* Def. Ex. 6 at 276:3-16. The "but for" test only requires that Plaintiffs prove that, but for their use of Lipitor, they would not have suffered the injuries they did, in this case, the development of diabetes in November, 2003 (for Ms. Daniels) and May, 2004 (for Ms. Hempstead); Dr. Handshoe testified as much, reiterating that, as set forth in his report, it was his opinion that "but for the taking of Lipitor, she would not have developed diabetes." *Id.* at 292:19-

23. That opinion, if believed, is sufficient for Ms. Daniels to prevail on her claims. If the jury concludes that, even without the Lipitor she took, Ms. Daniels would likely have developed diabetes at some later date, it presumably can adjust the damages it awards.

Pfizer also claims that Dr. Handshoe's opinions do not establish but-for causation for either Plaintiff because, presented with a hypothetical of 20 patients with identical risk factors and histories, he could not tell which hypothetical patient would have developed diabetes even if they had never taken statins. *See* Pfizer Br. at 31. But Pfizer's hypothetical patients have nothing to do with the actual real people, Ms. Daniels and Ms. Hempstead, whose medical records Dr. Handshoe reviewed and whose specific history of how and when they developed diabetes he studied. As to Ms. Daniels and Ms. Hempstead, Dr. Handshoe states unequivocally that, but for the Lipitor they ingested, they would not have developed diabetes. If these opinions are reliable – and, as demonstrated above, they are – Pfizer cannot have them excluded on the ground that they do not show what Dr. Handshoe specifically states they show.

Nor is it the case that the lack of "unique symptoms" for statin-induced diabetes renders any causation opinion meaningless, as Pfizer suggests. *See* Pfizer Br. at 31. If there *were* unique symptoms that differentiated statin-induced diabetes from other diabetes, no differential diagnosis would be needed. The same is true for every case where the differential diagnosis is used; the differential diagnosis method exists precisely because most causes do not leave behind a signature or biomarker to make clear the causal relationship. For example, in *Westberry,* there was no unique clinical symptom that differentiated the sinus infections the plaintiff there suffered as having been caused by the talcum powder on the gaskets his employer manufactured from any other sinus infection, but that did not preclude plaintiff's expert from opining that the talcum powder caused the infections. 178 F.3d at 263-64. Similarly, in *In re Actos (Pioglitazone) Products Liab. Litig.*, No. 12-CV-00064, 2013 WL 6825953, at *14 (W.D. La. Dec. 20, 2013), the court refused to exclude the specific causation opinion of plaintiff's expert, even though it did not appear there was any definitive way to identify plaintiff's bladder cancer as having been caused by his exposure to Actos, rather than some other cause.

In any event, Dr. Handshoe need not (and does not) opine that Lipitor was the sole cause of Plaintiffs' diabetes, *see Smith v. State Comp. Ins. Fund*, 749 P.2d at 464 (to prevail on causation, plaintiff must show that defendant's conduct was a "substantial factor" in producing the harm); *Hagen*, 816 S.W.2d at 670 ("substantial factor" test); *Nesselrode v. Executive Beechcraft, Inc.*, 707 S.W.2d 371, 381 (Mo. 1986) ("the proximate cause of an event or injury need only be a substantial factor or efficient causal agent"), nor even that he is 100% certain that, but for Lipitor, Plaintiffs would not have developed diabetes. It is sufficient for him to opine, *to a reasonable degree of medical certainty*, that Ms. Hempstead would not have developed diabetes when she did. *Pfeffer v. Kerr*, 693 S.W.2d 296, 30 (Mo. Ct. App. 1985) ("The standard for medical opinion concerning causation is usually said to be one of reasonable medical certainty."). For Ms. Daniels, even less certainty is required under Colorado law, where the opinion of an expert need only establish causation "within reasonable probability." *Morrison v. Indus. Claim Appeals Office of the State of Colo*., 760 P.2d 654, 655 (Colo. App. 1988) (claimant was not required to establish causation with reasonable medical certainty; evidence must establish causation "within reasonable probability.").That Dr. Handshoe's opinions are qualified, both as to the degree of certainty and as to the possibility of other contributing factors, does not mean they are insufficient to show but-for causation.

CONCLUSION

For the foregoing reasons, this Court should deny in its entirety Pfizer's motion to exclude the testimony of Dr. David Handshoe.

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Respectfully Submitted,

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